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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/016,737	01/30/1998	GERALD P. MURPHY	8511-007	7366

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	34

DATE MAILED: 08/20/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/016,737	MURPHY ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 May 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-37* is/are pending in the application.

4a) Of the above claim(s) *1-22,25 and 27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,26 and 28-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on **05/09/03** has been entered.

Accordingly, claims 23, 24, 26, and 28-37 are being examined.

The following are the remaining rejections.

OBJECTION

Claims 23 and 31 are objected to because claims 23 and 31 are confusing.

The specification discloses isolated dendritic cells are cultured in the presence of GM-CSF and IL-4, before exposure to the prostate antigen (specification, p. 22, under isolation of dendritic cells).

It is not clear whether in claims 23 and 31, the control isolated cell population comprising the "same number of cells that has not been exposed *in vitro* to the prostate antigen" also has been in culture medium containing GM-CSF and IL-4, similar to the cell population having an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen.

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, NEW MATTER, NEW REJECTION

Claims 23, 24, 26, and 28-37 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 23, 24, 26, and 28-37 are drawn to a composition comprising an isolated cell population exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, of at least 20 fold more, as compared to an isolated cell population comprising the "same number of cells that has not been exposed *in vitro* to the prostate antigen".

The specification does not disclose a composition comprising an isolated cell population exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, of at least 20 fold more, as compared to an isolated cell population comprising the "same number of cells that has not been exposed *in vitro* to the prostate antigen".

The specification only discloses that human DC's are isolated from peripheral blood of prostate cancer patients, and after about 7 days in culture, about 20-50 fold

higher numbers of DC's competent and able to activate prostate antigen specific T cells are recovered compared to those "directly isolated from peripheral blood" (p.10, second paragraph). There is no disclosure of the limitation of comparing to the "same number of cells" wherein "said cells have not been exposed *in vitro* to the prostate antigen", or a limitation drawn to "at least" 20 fold more".

REJECTION UNDER 35 USC 112, FIRST PARAGRAPH, SCOPE, NEW REJECTION

Claims 23, 24, 26, and 28-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising an isolated cell population cultured in the presence of GM-CSF and IL-4 and exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, of about 20 fold, as compared to an isolated cell population which is not cultured in the presence of GM-CSF and IL-4, does not reasonably provide enablement for a composition comprising an isolated cell population exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, of at least 20 fold more, as compared to an isolated cell population comprising the "same number of cells that has not been exposed *in vitro* to the prostate antigen". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 23, 24, 26, and 28-37 are drawn to a composition comprising an isolated cell population exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, of at least 20 fold more, as compared to an isolated cell population comprising the "same number of cells that has not been exposed *in vitro* to the prostate antigen".

Claims 23, 24, 26, and 28-37 encompass a composition comprising an isolated cell population cultured in the presence of GM-CSF and IL-4 and exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, of at least 20 fold more, as compared to an isolated cell population comprising the "same number of cells" that have been cultured in the presence of GM-CSF and IL-4, but that have not been exposed *in vitro* to the prostate antigen.

The specification discloses that human DC's are isolated from peripheral blood of prostate cancer patients, and after about 7 days in culture in the presence of GM-CSF and IL-4, about 20-50 fold higher numbers of DC's competent and able to activate prostate antigen specific T cells are recovered compared to those "directly isolated from peripheral blood" (p.10, second paragraph, p. 22, under Isolation of dendritic cells).

One cannot extrapolate the teaching in the specification to the claims, because if the control has the same number of cells that have been cultured in the presence of GM-CSF and IL-4, one would expect that culturing in the presence of GM-CSF and IL-4 would produce in the control the same number of dendritic cells, competent and able to

activate T cells specific to the prostate antigen as the claimed sample composition of dendritic cells, based on the disclosure in the specification.

Further, one would not expect that exposure of the competent dendritic cells to a prostate antigen would increase the number of said competent dendritic cells, because it is well known in the art that exposure of competent dendritic cells to an antigen only would activate said dendritic cells to present the antigen (Cohen et al, of record, column 12, paragraph under Treatment of cancer in a patient with autologous dendritic cells). There is no correlation between exposure to an antigen and production or increasing the number of competent dendritic cells.

In view of the above, it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly as claimed.

REJECTION UNDER 35 USC 102 (e)

Rejection under 35 USC 102 (e) of claims 23, 24, and 31-36 pertaining to anticipation by Cohen et al, as evidenced by Sallusto et al, Koski et al, and Czerniecki et al, remains for reasons already of record in paper No.30.

Applicant argues that Koski et al do not know or understand the mechanism by which monocytes are converted to the activated dendritic-cell like phenotype, and therefore the Koski reference cannot be used as extrincsic evidence that immature dendritic cells are present as an inherent property of calcium ionophore treatment of monocytes.

Applicant's arguments set forth in paper No.32 have been considered but are not deemed to be persuasive for the following reasons:

It is noted that Sallusto et al teach that dendritic cells (DCs) exist in two stages of maturation. Sallusto et al teach that as immature dendritic cells they are capable of antigen capture/processing and immunostimulation, but as they mature, they lose antigen-capturing capacity (p.1109).

It is further noted that Czerniecki et al teach that human peripheral blood contains a small population of immature dendritic cells distinguished from circulating monocytes by their low expression of CD14 (abstract). Czerniecki et al further teach that in fractrions 150-190 of elutriation (leukapheresis), a large percentage of cells, up to 28%, has the immature dendritic cell staining pattern (p.3825 second column, under results, and figure 1 on p. 3826).

In addition, it is noted that Cohen teach that pooled fractions 150, 160, 170, 180 and 190 from patients or donor leukapheresis are incubated for 40 hours in the presence autologous tumor cell lysate, for both cells untreated and treated with calcium ionophore (columns 11-12).

Thus regardless whether the mechanism by which monocytes are converted to the activated dendritic-cell like phenotype is known or not, i.e. whether monocytes treated with calcium ionophore would differentiate through the immature DC stage first before becoming mature DCs, a large percentage of cells in the pooled fractions 150, 160, 170, 180 and 190 from patients or donor leukapheresis taught by Cohen et al

would inherently comprise immature dendritic cells, as evidenced by Czerniecki et al, i.e. a large percentage of the untreated control cells and of treated cells at at least up to 4 hr after treatment with calcium ionophore would comprise immature DCs, and meet all the limitation of the claims.

Moreover, Cohen et al also teach that certain specific combination(s) of cytokines have been used successfully to amplify or partially substitute for the activation/conversion achieved with calcium ionophore. Cohen et al teach that these cytokines include GM-CSF, IL-2, IL-4 and IL-12, and that each cytokine when given alone is inadequate (column 10, lines 54-61, and table 3, on columns 12-13).

Thus the monocytes treated with a combination of cytokines, which include GM-CSF, IL-2, IL-4 and IL-12 would also produce immature DCs that maintain the antigen captureing and processing capacity, as evidenced by Sallusto et al.

REJECTION UNDER 35 USC 103, NEW REJECTION

1. Claims 23-24, 31-36 are rejected under 35 USC 103 as being obvious over Cohen et al (of record), in view of Sallusto et al, 1994 (of record), and Inaba K et al, Journal of experimental medicine (UNITED STATES) Jul 1 1987, 166 (1) p182-94..

Claims 23, 24, 31-36 are drawn to a composition comprising an isolated cell population exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, of at least 20 fold more, as compared to an isolated cell population comprising the same number of cells that has not been exposed *in vitro* to

the prostate antigen. The prostate antigen is a lysate of prostate tumor cells. The dendritic cells are immature dendritic cells, isolated from normal individual or from a prostate cancer patient. The activated T cells are CD4+ or CD8+.

The teaching of Cohen et al and Sallusto et al has been set forth in previous Office actions.

Cohen et al teach isolation of dendritic cells from peripheral blood from human normal individual and a patient with prostate cancer, by leukaphoresis and centrifugation (columns 5-6, and Examples 1-2). Cohen teach that pooled fractions 150, 160, 170, 180 and 190 from patients or donor leukapheresis are incubated for 40 hours in the presence autologous tumor cell lysate, for both cells untreated and treated with calcium ionophore (columns 11-12). Cohen et al teach that certain specific combination of cytokines have also been used successfully to partially substitute for the activation/conversion of the isolated cells to dendritic cells achieved with calcium ionophore. Cohen et al teach that these cytokines include rhGM-CSF, rhIL-2, reIL-4 and rhIL-12, and that each cytokine when given alone is inadequate for optimal upregulation (column 10, lines 54-60). Cohen et al teach that the enriched dendritic cells are incubated with a prostate tumor lysate, which activates the dendritic cells to present prostate tumor cell antigens. Cohen et al further teach that said dendritic cells after incubated with a prostate tumor lysate, and reintroduced into the patient could reduce the size of prostate tumor (Example 2).

Cohen et al do not teach that the number of dendritic cells are at least 20 fold more, as compared to an isolated cell population comprising the same number of cells

that has not been exposed *in vitro* to the prostate antigen. Cohen et al do not teach that the dendritic cells are immature dendritic cells. Cohen et al do not teach that the activated T cells are CD4+ or CD8+.

Sallusto et al teach that dendritic cells (DCs) exist in two stages of maturation. Sallusto et al teach that as immature dendritic cells they are capable of antigen capture/processing and immunostimulation, but as they mature, they lose antigen-capturing capacity (p.1109). Sallusto, F et al teach that the exposure to Granulocyte/Macrophage colony-stimulating factor plus interleukin 4 converts blood mononuclear cells to immature dendritic cells, that could efficiently present soluble antigen, such as tetanus toxoid to specific T cell clones (abstract). Sallusto, F et al further teach that cells grown with a combination of GM-CSF and TNF-alpha are inferior to those obtained with GM-CSF and IL-4, especially for presentation of soluble antigen (p.1111, first column, first paragraph).

Inaba K et al teach that dendritic cells activate CD4+ and CD8+ T cells.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to obtain dendritic cells, comprising exposing isolated blood mononuclear cells with a combination of cytokines comprising rhGM-CSF, rhIL-2, relL-4 and rhIL-12, or with Granulocyte/Macrophage colony-stimulating factor plus interleukin 4 as taught by Cohen et al, and Sallusto et al. One of ordinary skill in the art would have expected that the dendritic cells are immature dendritic cells that can effectively present a soluble antigen, such as prostate cancer antigen, and are able to activate specific T cells, because Sallusto et al teach that by culturing in GM-CSF and

interleukin-4, dendritic cell lines have been established from blood mononuclear cells that maintain the antigen capturing and processing capacity characteristics of immature dendritic cells *in vivo*, and because Cohen et al teach exposure of dendritic cells to prostate tumor cell lysate to activate the dendritic cells to present prostate tumor antigens. One of ordinary skill in the art would have expected that the yield of dendritic cells taught by Cohen et al and Sallusto et al would be at least 20 fold more, as compared to an isolated cell population comprising the same number of cells that has not been exposed *in vitro* to the prostate antigen, because the immature dendritic cells as taught by Sallusto et al and Cohen et al seem to be produced by the same process as disclosed in the specification of the instant invention, i.e. cultured in the presence of GM-CSF and IL-4 (specification, p.22, under isolation of dendritic cells). One of ordinary skill in the art would have expected that the dendritic cells taught by Cohen et al would activate CD4+ and/or CD8+ T cells , because activation of CD4+ and/or CD8+ T cells is a property of dendritic cells, as taught by Inaba K et al. The motivation is obvious, i.e. to use dendritic cells for treating prostate cancer, as taught by Cohen et al.

2. Claim 26 is rejected under 35 USC 103 as being obvious by Cohen et al (of record), in view of Sallusto et al, 1994 (of record), as applied to claims 23 and 24, and further in view of Lutz et al (of record).

Claim 26 is drawn to a composition comprising an isolated cell population exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, as compared to an isolated cell population comprising the same

number of cells that has not been exposed *in vitro* to the prostate antigen, wherein the dendritic cells are extended life span dendritic cells.

The teaching of Cohen et al and Sallusto et al has been set forth above.

Cohen et al and Sallusto et al do not teach that the dendritic cells are extended life span dendritic cells.

Luz et al teach making immortalized dendritic cells (Abstract), which overcomes the problem of being unable to maintain dendritic cells *in vitro* for long periods of time (p.278).

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the dendritic cells taught by Cohen et al and Sallusto et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would overcomes the problem of being unable to maintain dendritic cells *in vitro* for long periods of time, as taught by Luz et al.

3. Claims 28-29 are rejected under 35 USC 103 as being obvious by Cohen et al (of record), in view of Sallusto et al, 1994 (of record), as applied to claims 23 and 24, and further in view of Taylor et al (of record).

Claims 28-29 are drawn to a composition comprising an isolated cell population exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, as compared to an isolated cell population comprising the same number of cells that has not been exposed *in vitro* to the prostate antigen, wherein the dendritic cells have been cryopreserved prior to exposure *in vitro* to the prostate

antigen, and wherein said dendritic cells retain the abililty to take up and present antigen.

The teaching of Cohen et al and Sallusto et al has been set forth above.

Cohen et al do not teach that the dendritic cells are cryopreserved..

Taylor et al teach cryopreservation of dendritic cells, wherein said cryopreserved dendritic cells can be used in immunological procedures.

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to cryopreserve the dendritic cells taught by Cohen et al and Sallusto et al, using the cryopreservation method taught by Taylor et al. One of ordinary skill in the art would have been motivated to do so, to preserve the previously isolated dendritic cells.

4. Claim 30 is rejected under 35 USC 103 as being obvious by Cohen et al (of record), in view of Sallusto et al, 1994 (of record), as applied to claims 23 and 24, and further in view of Taylor et al (of record), as applied to claims 28-29, and Lutz et al.

Claim 30 drawn to a composition comprising an isolated cell population exposed *in vitro* to a soluble prostate antigen, the cell population has an increased number of human dendritic cells, competent and able to activate T cells specific to the prostate antigen, as compared to an isolated cell population comprising the same number of cells that has not been exposed *in vitro* to the prostate antigen, wherein the dendritic cells have been cryopreserved prior to exposure *in vitro* to the prostate antigen, wherein said dendritic cells retain the abililty to take up and present antigen, and wherein the dendritic cells are extended life dendritic cells.

The teaching of Cohen et al and Sallusto et al and Taylor et al has been set forth above.

Cohen et al, Sallusto et al and Taylor et al do not teach that the dendritic cells have extended life.

Luz et al teach making immortalized dendritic cells (Abstract), which overcomes the problem of being unable to maintain dendritic cells *in vitro* for long periods of time (p.278).

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to immortalize the cryopreserved dendritic cells taught by Cohen et al, Sallusto et al, and Taylor et al, using the immortalizing method taught by Luz et al, because immortalizing dendritic cells would overcomes the problem of being unable to maintain dendritic cells *in vitro* for long periods of time, as taught by Luz et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

July 25, 2003